

# Management of diabetes during Ramadan: The potential of newer interventions

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**In this article the authors review the potential complications of fasting during Ramadan and summarise the currently available guidelines. They also assess the potential of newer interventions, including patient education programmes and drug treatments, to help improve the management of people with diabetes who are fasting during Ramadan.**

Ramadan is the holiest month in the Islamic calendar; it is when adult Muslims who are able to do so abstain from any food and drink (including the intake of medication) between sunrise and sunset. Ramadan is the ninth month of the Islamic lunar calendar, and each year sees it fall 10 or 11 days earlier in the solar calendar. This means that there are phases when Ramadan falls in the summer (as is currently the case) and the longer hours of daylight can result in a fasting period of up to 20 hours. While people with diabetes who fast during Ramadan need careful management every year, the prolonged fasting periods in the current period means that clinicians need to be even more aware of the implications for the people they see who have diabetes.

## Complications of fasting during Ramadan Hypoglycaemia

Hypoglycaemia is a major potential complication of prolonged fasting in people with diabetes, and during Ramadan this can be a significant issue. A number of studies have demonstrated increased episodes of hypoglycaemia during Ramadan (e.g. Loke et al, 2010; Ahmad et al, 2012). Of particular note is the EPIDIAR (Epidemiology of Diabetes and Ramadan) study (Salti et al, 2004). This was a multi-centre, international, observational study that analysed over 12 000 individuals, and it found an increase in hypoglycaemic episodes that was greater than four-fold in type 2 diabetes and seven-fold in type 1 disease (comparing Ramadan with other months). Individual case reports also illustrate that some episodes of hypoglycaemia during Ramadan

can be devastating, with complications such as stroke (Chowdury, 2011).

## Hyperglycaemia and diabetic ketoacidosis

Perhaps what is less well known is the increased risk of hyperglycaemia and even ketoacidosis in people with diabetes who fast during Ramadan. The EPIDIAR study (Salti et al, 2004) showed a five-fold increase in the incidence of severe hyperglycaemia (requiring hospitalisation) during Ramadan, relative to other months, in people with type 2 diabetes, and a three-fold increase in people with type 1 diabetes. This increase was thought to be due to people reducing or omitting medication because of the fear of hypoglycaemia, as well as changes in dietary intake (including a high calorie intake of sugary foods on breaking the fast).

There is some theoretical basis to an increased risk of diabetic ketoacidosis (DKA) linked to prolonged fasting (increased glucagon production and increased hypoinsulinaemia resulting in increased glucose levels and lipolysis). Although the EPIDIAR study did report some episodes of DKA in people with type 1 diabetes during Ramadan, other studies (Abusweril et al, 2003; Rafik et al, 2009) have not shown an increased risk of DKA or mortality in this group.

## Dehydration and thrombosis

A lack of fluid intake can lead to dehydration in fasting individuals, particularly in hot climates and in those undertaking manual work. Dehydration can also be exacerbated by an osmotic diuresis in people who have hyperglycaemia as a result of poor

**Citation:** Farooqi A, Khunti K, Rameez M, Farooqi I (2013) Management of diabetes during Ramadan: The potential of newer interventions. *Diabetes & Primary Care* 15: 303–7

## Article points

1. Ramadan offers an opportunity to promote lifestyle improvement as well as raising awareness of the risks of hypoglycaemia among Muslims with diabetes.
2. It is important that individuals make an informed choice on whether to fast or not and are aware of their personal risks.
3. Clinicians and diabetes educators should plan for Ramadan-specific education that is appropriate for their population. In areas with a large Muslim population, this should be a routine part of existing education programmes.
4. Newer agents may offer some clinical benefits in Ramadan with regard to hypoglycaemia, although cost considerations and the need for more long-term data should be taken into account.

## Key words

- Newer drugs
- Patient education programmes
- Ramadan

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### Page points

1. A range of guidance is available for healthcare professionals on how to help people manage their diabetes during Ramadan.
2. Current guidance suggests that people with diabetes should amend medication to take account of the usually smaller morning meal (sahur [also known as sehri]), the larger evening meal (iftar) and the prolonged fast between the two.

compliance with medication and dietary advice during Ramadan (Al-Arouj et al, 2010).

A consequence of dehydration can be a hypercoagulable state, with impaired fibrinolysis and potentially an increased risk of thrombosis.

### Other risks

Existing studies, many of which are small scale, show inconsistent results on the impact of Ramadan on exercise levels, body weight and other risk factors such as blood pressure and lipid levels (Al-Arouj et al, 2010). Such changes may impact on longer-term clinical outcomes and are worthy of further research.

### Review of current guidance

A range of guidance is available for healthcare professionals on how to help people manage their diabetes during Ramadan. This includes guidance published by: Al-Arouj et al (2005; 2010 [an update]) in collaboration with the American Diabetes Association; Hui et al (2010a), in the *British Medical Journal*; and many local diabetes services where there are significant numbers of Muslim residents (e.g. Bedfordshire Diabetes, 2010; Leicestershire Diabetes, 2011b).

These guidelines all stress certain key elements to supporting patients who are considering fasting during Ramadan. This includes assessment of the risk of fasting, education of people with diabetes and modification of therapies, each of which is considered below.

### Assessment of the risk of fasting

Assessment of the risk of fasting allows appropriate advice to be given to people with diabetes. High risk individuals, such as those with poor glycaemic control, those with recent episodes of severe hypoglycaemia or DKA or those with complications such as renal failure, should, in our opinion, be advised not to fast. Individuals who may be able to fast but require detailed advice and monitoring include those who have acceptable control but take medications that can cause hypoglycaemia, such as insulin or sulphonylureas (SUs). Lower-risk individuals who may be able to fast more safely include those well controlled on diet only or on a monotherapy with a low risk of hypoglycaemia such as metformin. Ultimately, fasting is a decision for people with diabetes to take; the role of the

healthcare professional is to ensure that they are able to make an informed choice, are aware of the risks, and are appropriately supported in order that, if they choose to fast, they can do so as safely as possible.

### Education of people with diabetes

Hui et al (2010a) recommend that patient education for Ramadan should encompass advice on diet and meal planning, exercise, blood glucose monitoring and the recognition and management of complications.

### Modification of therapies

Current guidance (as discussed above) suggests that people with diabetes should amend medication to take account of the usually smaller morning meal (sahur [also known as sehri]), the larger evening meal (iftar) and the prolonged fast between the two.

The modification of drug therapy will be dependent on the individual and his or her lifestyle and dietary habits during Ramadan (as it is at any other time). Many people will have complex treatment issues or long-standing diabetes and thus typically be taking several agents to help them achieve good glycaemic control. The evidence on combinations of drugs during Ramadan is limited, but the guidance documents do offer general advice about the benefits or problems associated with individual agents, which can be helpful to clinicians and people with diabetes.

The consensus from the guidance discussed above is that oral agents that are not, in isolation, associated with an increased risk of hypoglycaemia, such as metformin, can be safely used, but that they are best given as follows: with the main meal, if once daily; or, if more than once daily, as divided doses with (if appropriate) the larger dose being taken with the main meal at iftar.

Greater care needs to be taken with drugs that increase the risk of hypoglycaemia, such as SUs. Although there are no convincing studies that show these drugs result in more hypoglycaemia during Ramadan, the consensus is that, if chosen, shorter-acting SUs such as gliclazide are preferable and that there should be a reduction of the morning dose taken at sahur.

Insulin secretagogues such as repaglinide and nateglinide, with their short duration of action, are an option for some people with type 2 diabetes

during Ramadan, but evidence of overall efficacy is limited.

The recommendations for insulin (e.g. Al-Arouj et al, 2010) are that doses be reduced depending on the particular regimen. Once-daily basal doses should be reduced by one-third and administered with either the morning or the evening meal, as is usual for the individual. For twice-daily regimens (biphasic insulins), there should be a dose reduction of 50% with each meal.

Basal–bolus regimens are more complex but the advice for the basal element should be followed and the bolus amount should be decreased by 50% at each meal, with adjustments of additional bolus doses (which may be required, for example, around midnight) depending on blood glucose monitoring results.

Doses of biphasic insulins (e.g. 50/50 and 30/70 pre-mixes) will need to be reduced by at least half. One study has suggested that because of the pattern of eating during Ramadan, a 50/50 pre-mix offered superior glycaemic control to a 30/70 pre-mix (Hui et al, 2010b).

It is important that newly introduced agents and other changes in regimens are tested prior to Ramadan; this will allow for an assessment of side effects and, in our experience, can also allow minor side effects to subside. Trial runs of fasting days may help educate people with diabetes on the impact of fasting (for example, on their glucose levels) prior to Ramadan.

### The place of newer interventions

The management of diabetes in the past decade has been characterised by the emergence of newer interventions. These have included the increasing recognition of the importance of self-management, with the development of patient education programmes, as well as the emergence of therapies based on the incretin pathway and sodium–glucose cotransporter 2 (SGLT2) and novel insulins.

#### Newer non-pharmacological interventions: Patient education

There are a number of important issues regarding fasting during Ramadan that can be addressed through more effective patient education. This includes supporting people with diabetes to make an informed decision on whether to fast or not, helping

individuals manage their diabetes more effectively during Ramadan if they are fasting, and using the experience of Ramadan to improve longer-term management of the condition.

#### To fast or not to fast?

While it is religiously acceptable that Muslims who are sick or at high risk can be exempt from fasting during Ramadan, the reality, however, is that most Muslims with diabetes choose to fast. This includes many with type 1 disease and those who are at significant risk of complications (Salti et al, 2004). For many Muslims the spiritual, psychological and social reasons for fasting will override any medical concerns; it may be that some individuals do not fully understand the risks to their health. This is a poorly understood and potentially sensitive subject that requires further research on how best to help people to make informed choices on fasting.

#### Improving self-management during Ramadan

A number of patient education programmes have been developed to help people manage their diabetes during Ramadan (Chowdury et al, 2003; Hassanein et al, 2009). These focus on advice regarding diet, blood glucose monitoring, medication and managing complications such as hypoglycaemia.

While these programmes, where they exist, are undoubtedly valuable to the individuals who access them, the challenge is to ensure that all Muslims with diabetes receive such support. Future research on how to ensure wider uptake – perhaps through group education sessions in accessible settings, by incorporation into standard diabetes education programmes (e.g. DESMOND; Leicestershire Diabetes, 2011a), and within routine diabetes reviews – is important in ensuring wider dissemination.

Where there are large populations of Muslims there need to be systematic and continuous programmes of activity to ensure that general practices, for example, are not overwhelmed by people seeking advice just before Ramadan.

#### Ramadan and potential longer-term benefit

Ramadan can be a deeply spiritual time for Muslims, when they are particularly open to reflection and self-improvement. Programmes that have utilized this time to modify health behaviours include smoking-

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cessation promotions. The potential that Ramadan offers to improve understanding of diabetes and self-management for longer-term benefit has not really been explored and requires further study.

### Newer pharmacological interventions

#### DPP-4 inhibitors

Agents in this class act on the incretin pathway and enhance the action of glucagon-like peptide-1 (GLP-1) by inhibition of dipeptidyl peptidase-4. Sitagliptin, the first agent in the class, received its UK licence in 2007. The current place of DPP-4 inhibitors in UK practice is generally third line, after SUs and metformin, although they may be used in a second-line setting where SUs are contraindicated (NICE, 2009).

DPP-4 inhibitors are a potentially useful drug for use in Ramadan as they are not associated with hypoglycaemia, unless used in combination with other antidiabetes agents.\* A number of studies have shown the benefits of sitagliptin and vildagliptin, compared with SUs, as a second-line add-on to metformin in significantly reducing hypoglycaemia during Ramadan (Devendra et al, 2009; Al Sifri et al, 2011; Hassanein et al, 2011).

Clinicians may consider that in Muslims who wish to go on to fast during Ramadan, DPP-4 inhibitors should be used as a second-line add-on therapy to metformin in preference to SUs (at least based on currently available evidence).

#### GLP-1 receptor agonists

There are a number of injectable GLP-1 receptor agonists available for type 2 diabetes, with the first, exenatide twice daily, licensed in the UK in 2006. These agents improve glycaemic control without an increased risk of hypoglycaemia, unless used in

\*See <http://medicines.org.uk/emc/medicine/19609>, <http://medicines.org.uk/emc/medicine/20734>, <http://medicines.org.uk/emc/medicine/22315> and <http://medicines.org.uk/emc/medicine/25000> (accessed 14.11.13).

†See <http://medicines.org.uk/emc/medicine/19257>, <http://medicines.org.uk/emc/medicine/21986>, <http://medicines.org.uk/emc/medicine/24665>, <http://medicines.org.uk/emc/medicine/27405> and <http://medicines.org.uk/emc/medicine/27406> (accessed 14.11.13).

‡See <http://medicines.org.uk/emc/medicine/27188> (accessed 14.11.13).

§See <http://medicines.org.uk/emc/medicine/27359>, <http://medicines.org.uk/emc/medicine/27360> and <http://medicines.org.uk/emc/medicine/27363> (accessed 14.11.13).

combination with other antidiabetes agents, and can also be associated with a sustained weight loss.† However, there is little literature on their use in Ramadan. One report indicated that exenatide can be used in Ramadan, but that doses of SUs, if used in conjunction, may need to be reduced (Bravis et al, 2010).

Further studies regarding the use of GLP-1 receptor agonists in Ramadan are needed to identify its optimum role.

#### SGLT2 inhibitors

The first SGLT2 inhibitor, dapagliflozin, was licensed in the UK in 2013 for use as monotherapy or in a specified combination with other agents in type 2 diabetes.‡ For this agent – and other drugs in the class in development – there is a novel mode of action: the lowering of blood glucose levels by reducing renal re-absorption of glucose, via SGLT2 inhibition. Dapagliflozin *per se* is not associated with significant hypoglycaemia,‡ and it may therefore be of potential value as a glucose-lowering drug for use during Ramadan. Specific studies are needed to establish this.

It should also be noted that dapagliflozin can lead to an osmotic diuresis,‡ and the risk of volume depletion during a prolonged fast might be a significant contraindication to its use in Ramadan.

#### Insulin analogues

Insulin analogues include rapid-acting and long-acting preparations. The latest addition to this group of therapies is insulin degludec, which is taken once daily, preferably at the same time each day, but with some flexibility in the daily pattern if needed (a minimum of 8 hours between injections should always be ensured).§

An important advantage of the short-acting insulin analogues is their faster mode of action and their targeting of reductions in postprandial glucose (Hirsch, 2005). One of the advantages of longer-acting insulin analogues is in reducing the risk of hypoglycaemia compared with human insulins (Barnett, 2003).

Studies of insulin analogues used in Ramadan, although short term, do provide some evidence that they are advantageous in terms of reduced episodes of hypoglycaemia and improved glycaemic control (Kadiri et al, 2001; Kassem et al, 2005).

### Insulin pump therapy

Studies conducted in the Middle East (Bin-Abbas, 2008; Benbarka et al, 2010) have shown that insulin pump users, including younger people, can fast safely during Ramadan. Insulin pumps offer the flexibility to adjust the dose of insulin according to blood glucose levels and therefore minimise hypoglycaemia risk.

Studies in Ramadan have been relatively small scale and been accompanied by intensive support for users. They have largely been undertaken in Middle Eastern countries, where, because of the latitude, the fasting period is not as prolonged as in the UK. Feasibility studies in countries such as the UK have yet to be undertaken.

### Conclusion

Awareness of the risks of prolonged fasting is important for people with diabetes. Many Muslims with diabetes desire to fast during the Ramadan period and there is the potential for them to safely do so providing that they are given appropriate advice and guidance. We believe that clinicians need to devise strategies that ensure that general advice is available to lower-risk individuals and that specific personal advice is available for those at higher risk of problems; the scope of this challenge will vary with the size of the local Muslim population. Working with local religious leaders has the potential to help encourage those who are at high risk of complications to avoid fasting.

Newer agents that are associated with a lower risk of hypoglycaemia than some older therapies offer the potential for more Muslims with diabetes to fast safely during Ramadan. Cost issues and the limited nature of evidence on the use of newer agents in Ramadan are important considerations. Nevertheless, we believe that the potential benefits of newer agents should certainly be taken into account by clinicians when individualising management. ■

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